

Elizabethkingia meningoseptica bacteremia in immunocompromised hosts: The first case series from India

Abdul Ghafur, P. R. Vidyalakshmi, K. Priyadarshini, Jose M. Easow¹, Revathi Raj¹, T. Raja²

Abstract

Background: Although *Elizabethkingia meningoseptica* (*Chryseobacterium meningosepticum*) infections in immunocompromised hosts have been recognised, clinical data detailing these infections remain limited, especially from India. Antimicrobial susceptibility data on *E. meningoseptica* remain very limited, with no established breakpoints by Clinical and Laboratory Standards Institute (CLSI). The organism is usually multidrug resistant to antibiotics usually prescribed for treating Gram-negative bacterial infections, a serious challenge to the patient and the treating clinicians. **Materials and Methods:** The analysis was done in a tertiary care oncology and stem cell transplant center. Susceptibility testing and identification of *E. meningoseptica* was done using Vitek auto analyzer. Records of immunocompromised patients with *E. meningoseptica* bacteremia were analysed from January 2009 to March 2012. **Results:** A total of 29 *E. meningoseptica* bacteremia cases were documented between 2009 and 2012. Eleven patients were immunocompromised. Three were post stem cell transplant and one was post cord blood transplant. The mean age of the patients was 48.4 years. Mean Charlson's comorbidity index was 5.7. Four had solid organ malignancies, five had hematological malignancies, and two had lymphoreticular malignancy. Eight patients had received chemotherapy. Mean Apache II score was 18. Mean Pitts score for bacteremia was 4.7. Two were neutropenic (one post SCT, one MDS post chemo) with a mean white blood cell (WBC) count of 450/mm³. Ten had a line at the time of bacteremia. Mean duration of the line prior to bacteremia was 8 days. Eight had line-related bacteremia. Three had pneumonia with secondary bacteremia. All received combination therapy with two or more antibiotics which included cotrimoxazole, rifampicin, piperacillin–tazobactam, tigecycline, or cefepime–tazobactam. All the isolates showed *in vitro* resistance to ciprofloxacin. Five patients died, but a multivariate analysis was not done to calculate the attributable mortality. **Conclusion:** In our study, central line was the commonest risk factor for *E. meningosepticum* bacteremia, although a multivariate analysis was not done. There has not been much of a change in the susceptibility pattern of these organisms over 3 years, with good susceptibility to piperacillin–tazobactam and cotrimoxazole. Even though uncommon, *E. meningoseptica* is an important pathogen, especially in immunocompromised hosts with indwelling devices.

Key words: Bacteremia, *Chryseobacterium meningosepticum*, *Elizabethkingia meningoseptica*, immunocompromised host

Introduction

Elizabethkingia meningoseptica (*Chryseobacterium meningosepticum*) is a ubiquitous Gram-negative bacillus described by Elizabeth O. King in 1959.^[1] Although *E. meningoseptica* infections in immunocompromised hosts are a well-known entity,^[2] limited clinical data are available from the Indian subcontinent. This organism is usually resistant to most antibiotics prescribed for treating Gram-negative bacterial infections, including extended-spectrum beta-lactam agents and aminoglycosides, a serious challenge to the patient and the treating clinicians.^[3]

Departments of Infectious Diseases, ¹Hemato-Oncology, ²Oncology, Apollo Speciality Hospitals, Chennai, India

Correspondence to: Dr. Abdul Ghafur,
E-mail: drghafur@hotmail.com

Antimicrobial susceptibility data on *E. meningoseptica* also remains very limited, with no established breakpoints by Clinical and Laboratory Standards Institute (CLSI).^[4]

Materials and Methods

The analysis was done in a tertiary care oncology and stem cell transplant center. Bacterial identification was done by using mini API strips – Rapid ID32E and ID32GN (bioMerieux) from January 2011 to May 2011 and thereafter by using VITEK2 compact system. Susceptibility testing was performed by a standardised disk diffusion method according to CLSI guidelines on Muller Hinton agar from January 2009 to May 2011.^[5,6] From June 2011 to March 2012, susceptibility testing was performed by using the instrument VITEK2 compact. As there is no established breakpoint for *Chryseobacterium* by CLSI, the interpretive breakpoints for *Pseudomonas* were used. For tigecycline, the breakpoint for *Enterobacteriaceae* was used.^[7]

The institutional ethics committee approval was obtained prior to analysis and publication.

The isolates were tested against piperacillin–tazobactam 100/10 µg, gentamicin 10 µg, amikacin 30 µg, netilmycin 30 µg, ceftazidime 30 µg, cefoperazone–sulbactam 75/30 µg, cefepime 30 µg, cefepime/tazobactam 30/10 µg, imipenem 10 µg, meropenem 10 µg, ciprofloxacin 5 µg,

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trimethoprim/sulfamethoxazole 1.25/23.75 µg, and tigecycline 15 µg. While clear-cut CLSI guidelines are available for Enterobacteriaceae and *Pseudomonas*, the breakpoint of the most of the antibiotics, the guidelines for antibiotics such as cefoperazone–sulbactam and cefepime/tazobactam are not elucidated in the current CLSI guidelines. Hence, the breakpoints of cefoperazone and cefepime were applied for cefoperazone/sulbactam and cefepime/tazobactam, respectively. Antibiotic disks were obtained from BD BBL (USA), Oxoid (UK), and HiMedia Lab (India).

Only the records of patients who had a solid organ, hematological, and lymphoreticular malignancy with *E. meningoseptica* bacteremia were analysed from January 2009 to March 2012. Patient details like age, sex, underlying immunocompromising condition with comorbidities, chemotherapeutic agents used, ICU stay, and central line (both central line and peripheral line samples grew *Chryseobacterium* with no other identifiable source) were looked into. Pitt's bacteremia score and Charlson comorbidity index were calculated for all patients. Outcome of the patients (28-day mortality) was also analysed; however, the attributable mortality was not calculated.

Results

A total of 29 cases with *E. meningoseptica* bacteremia were documented between 2009 and 2012. Eleven patients were immunocompromised [Figure 1]. The mean age of the patients was 48.4 years. Seven were males and four were females. Mean Charlson's comorbidity index was

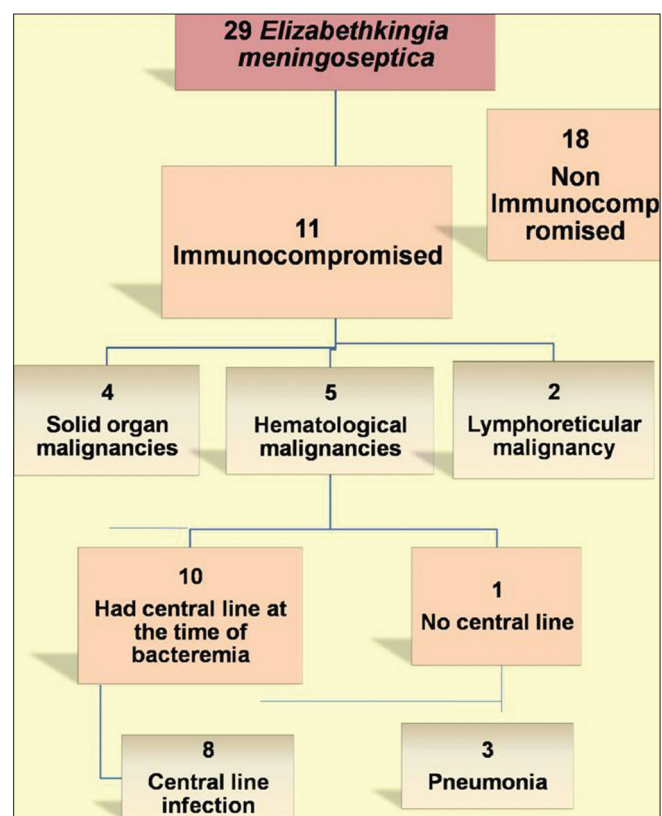


Figure 1: Analysis of patients with *Chryseobacterium*

5.7. Four of them had solid organ malignancies, five had hematological malignancies, and two had lymphoreticular malignancy. Eight patients had received chemotherapy. Three patients were post stem cell transplant and one patient was post cord blood transplant. Eight patients had history of a recent hospitalization. At the time of bacteremia, eight patients were in the ICU. Mean Apache II score was 18. Mean Pitt score for bacteremia was 4.7. Out of the 11 patients, 2 were neutropenic (one post Stem Cell transplant, one Myelodysplastic Syndrome post chemo) with a mean white blood cell (WBC) count of 450/mm³. Mean WBC among non-neutropenics was 10,833/mm³ (range 2300–19,200) and the mean neutrophil count was 75% (range 2500–15,754; mean 7441). Six patients required mechanical ventilation. Ten patients had a line at the time of bacteremia. Mean duration of the line prior to bacteremia was 8 days. Eight out of the 11 patients had line-related bacteremia. Three patients had pneumonia with secondary bacteremia. All the patients received combination therapy with two or more antibiotics, which included cotrimoxazole, rifampicin, piperacillin–tazobactam, tigecycline, or cefepime–tazobactam. All the isolates showed *in vitro* resistance to ciprofloxacin. Ten isolates were susceptible to piperacillin–tazobactam and cotrimoxazole. Six isolates were sensitive to tigecycline. Mean duration of therapy was 10 days. Five out of the eight isolates tested were sensitive to cefepime–tazobactam. Five out of 11 patients died, but a multivariate analysis was not done to calculate the attributable mortality. Clinical and laboratory details of the patients are elaborated in Table 1a,b,c.

Discussion

E. meningoseptica is associated primarily with meningitis in neonates and a variety of infections in immunocompromised patients. Clinical data detailing these infections remain limited. Infections with *E. meningoseptica* are not very common; however, they are clinically important as the organism is intrinsically resistant to multiple antibiotics which are routinely used to treat a patient with suspected sepsis.^[2] Infections that have been reported with *C. meningoseptica* are pneumonia, meningitis, and catheter-related blood stream infections. However, there have been cases of biliary sepsis, osteomyelitis, and keratitis in the literature as well.

Environmental studies have shown *Chryseobacteria* can survive in chlorine-treated water. They often are found to colonise sink basins and taps and in ventilator tubing. They can also colonise patients via contaminated medical equipments involving fluids, for example, respirators, intubation tubes, humidifiers, incubators for newborns, ice chests, and syringes.^[8-10] Surgically implanted devices such as intravascular catheters and prosthetic valves can also be contaminated with this organism.^[8-10]

Infections with *C. meningoseptica* have been associated with prolonged hospitalisation, prior exposure to multiple antibiotics, and immunocompromised host.^[11] Our series analysed bacteremic isolates only and the main source

Table 1: Clinical and laboratory details of the patients

Patient no.	1	2	3	4	5	6	7	8	9	10	11
Age	57	40	3	40	73	70	62	66	7	65	48
Gender	M	F	M	F	M	M	M	M	M	F	F
Diagnosis	Myelodysplastic syndrome	Hodgkin's lymphoma post stem cell transplant	Bilineage leukemia post stem cell transplant	AML post stem cell transplant	Multiple myeloma	Carcinoma prostate	Ca lung	Non hodgkins lymphoma	Bileage leukemia/ cord blood transplant/ gyvhd	Squamous cell carcinoma right alveolus	Ca ovary- metastatic disease
Recent hospitalisation	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No
Chemo received	Nil	Bendamustine/ cytarabine/ melphalan/ etoposide	Tacrolimus/ pangraf/ cytarabine	Cyclosporin/ steroids	Bortizomib/ melphlan, prednisolone	Docetaxel	Gemtinib/ erlotinib	Mabthera/ endoxan, vincristin, adriamycin	Dasatanib/ pangraf	Nil	Nil
ICU stay	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Apache score	34	8	0	12	14	12	31	32	0	18	33
Total count	700	200	4200	14300	16700	5800	19200	7800	2300	14600	9600
Differential count			N-60, L-22	N-51, L-5	N-89	N-89	N-82	N-84	N-79	N-72	N-70
Charlson's co-morbidity index	7	5	2	2	8	9	7	8	5	2	8
Mechanical ventilation	Yes	No	No	Yes	Yes	Yes	Yes	Yes	No	Yes	No
Line	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Line days	2	16	15	9	8	4	6	6	90	0	14
No of icu days prior to bacteremia	2	3	0	6	12	12	13	8	0	1	6
Renal failure	Yes	No	No	No	Yes	No	Yes	Yes	No	No	Yes
Source	Pneumonia	Line	Line	Pneumonia	Line	Line	Line	Line	Line	Pneumonia	Line
Treatment	Cefipime+ tazobactam, tigecycline, cotrimoxazole	Cefipime+ tazobactam, rifampicin/ teicoplanin	Pipracillin+ tazobactam, cotrimoxazole	Pipracillin+ tazobactam, cotrimoxazole	Pipracillin+ tazobactam, cotrimoxazole	Cotrimoxazole, tigecycline	Cotrimoxazole, tigecycline	Cotrimoxazole, tigecycline, rifampicin	Tigecycline/ teicoplanin/ piperacillin+ tazobactam	Cefipime+ tazobactam, cotrimoxazole, rifampicin	Piperacillin- tazobactam, cotrimoxazole
Duration of therapy	4	14	14	10	12	8	9	6	14	11	8
Microbiological clearance	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No
Outcome	Survived	Survived	Survived	Survived	Survived	Expired	Expired	Expired	Expired	Survived	Expired

for bacteremia was the central line (8 out of 11) followed by pneumonia. *C. meningosepticum* was the second most common cause of Gram-negative infection in a dialysis unit as per a Greek study.^[12] The same study also showed that *Pseudomonas aeruginosa* was the most prevalent isolate in all types of water samples, followed by *C. meningosepticum* in tap and treated water and by *Escherichia coli* in dialysate.^[12]

A study from Taiwan on the analysis of adult patients with *E. meningoseptica* bacteremia showed that 86% of the patients had nosocomial infections and 60% had acquired the infection in the ICUs, and the most common underlying diseases were malignancy (36%) and diabetes mellitus (25%). This study showed a 14-day mortality of 23.4%.^[13]

In our study, 8 out of the 11 patients were in the ICU at the time of development of bacteremia. All patients in our series, being oncology patients, were immunocompromised. In our study, 5 out of 11 patients died. However, the attributable mortality was not calculated.

Multivariate analysis from studies have shown that *E. meningoseptica* bacteremia acquired in an ICU and presence of effective antibiotic treatment after the availability of culture results were independent predictors of 14-day mortality.^[7] *E. meningoseptica* infection is very challenging as the organism is inherently multidrug resistant and only a limited range of antibiotic classes are available for treatment. Studies have shown that susceptibility of the isolates was relatively high (>50%) only to piperacillin, piperacillin-tazobactam, trimethoprim-sulfamethoxazole, and ciprofloxacin. More than 80% of the isolates tested were susceptible to trimethoprim-sulfamethoxazole, moxifloxacin, and levofloxacin.^[7] Our study showed similar susceptibilities except for fluoroquinolones where all the 11 isolates showed *in vitro* resistance to ciprofloxacin. Ten isolates were susceptible to piperacillin-tazobactam and cotrimoxazole. Six isolates were sensitive to tigecycline. Five out of the eight isolates tested were sensitive to cefepime-tazobactam. Rifampicin and cotrimoxazole may be used in the treating regimen.^[14,15] Rifampin was active against the majority of strains in an *in vitro* study. Hence, rifampicin can be used in combination to treat severe invasive infections.^[16] Many studies have shown that vancomycin has marginal *in vitro* activity against *Chryseobacterium* spp. isolates. There are reports of successful usage of vancomycin to treat *Chryseobacterium* infections.^[16-18] However, when the isolates were tested for vancomycin susceptibility, a majority of the isolates showed an intermediate susceptibility.^[10]

C. meningosepticum is a biofilm-forming organism. Various studies have shown that mortality is associated with the use of central venous catheters, initial inappropriate antimicrobial therapy, and higher biofilm production by the organism. The outcome of patients with biofilm-forming *C. meningoseptica* infection was adversely affected by the choice of inappropriate antimicrobial therapy and the use of

long-term indwelling intravascular catheters.^[19] Presence of effective antibiotic treatment after the availability of culture results was an independent predictor of 14-day mortality. The 14-day mortality was higher among patients receiving carbapenems than fluoroquinolones or other antimicrobial agents.^[7]

Conclusions

In our series of oncology patients, central line was the commonest risk factor for *E. meningoseptica* bacteremia, although a multivariate analysis was not done. There has not been much of a change in susceptibility pattern of this organism over 3 years, with good susceptibility observed to piperacillin-tazobactam and cotrimoxazole. In contrary to other studies, all our isolates were ciprofloxacin resistant. Even though uncommon, *E. meningoseptica* is an important pathogen, especially in immunocompromised hosts with indwelling devices.

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